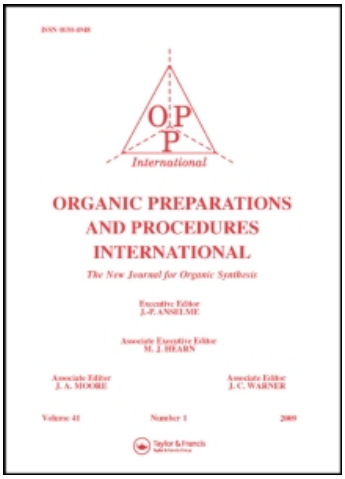

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SOLID-PHASE SYNTHESIS OF DIFLUOROBENZIMIDAZOLES AND DIFLUORO-2-QUINOXALINOLS

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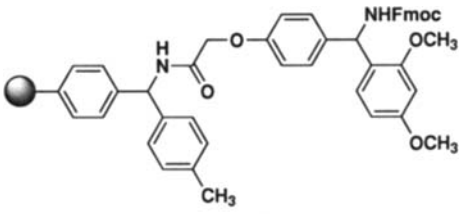
Over the history of drug discovery, heterocyclic structures often show interesting features and display favorable biological activity. Most approved therapeutic agents as well as drug candidates are derived from heterocyclic compounds. As solid-phase organic synthesis holds some important advantages over solution-phase procedure, not surprisingly more than 80% of combinatorial syntheses are performed on solid support.[1] In particular, because of the tremendous functional diversity and drug-like potentials, current interest in solid-phase chemistry is focussed on small heterocycles.[2] Therefore, the systematic study of solid-phase chemistry is still an important area of investigation.

Benzo-fused bicyclic heterocycles such as benzimidazoles, 2-quinoxalinols and quinoxalinones, which have been designated as privileged structures,[3] have exhibited a wide range of biological activities and have been reported frequently in the field of solid-phase chemistry.[4-15] It is well known that the C-F bond is isosteric with the C-H bond and fluoro analogues often display improved pharmacodynamic properties. However, only a few reports on the preparation of fluoro skeletons have appeared.[4,16,17]

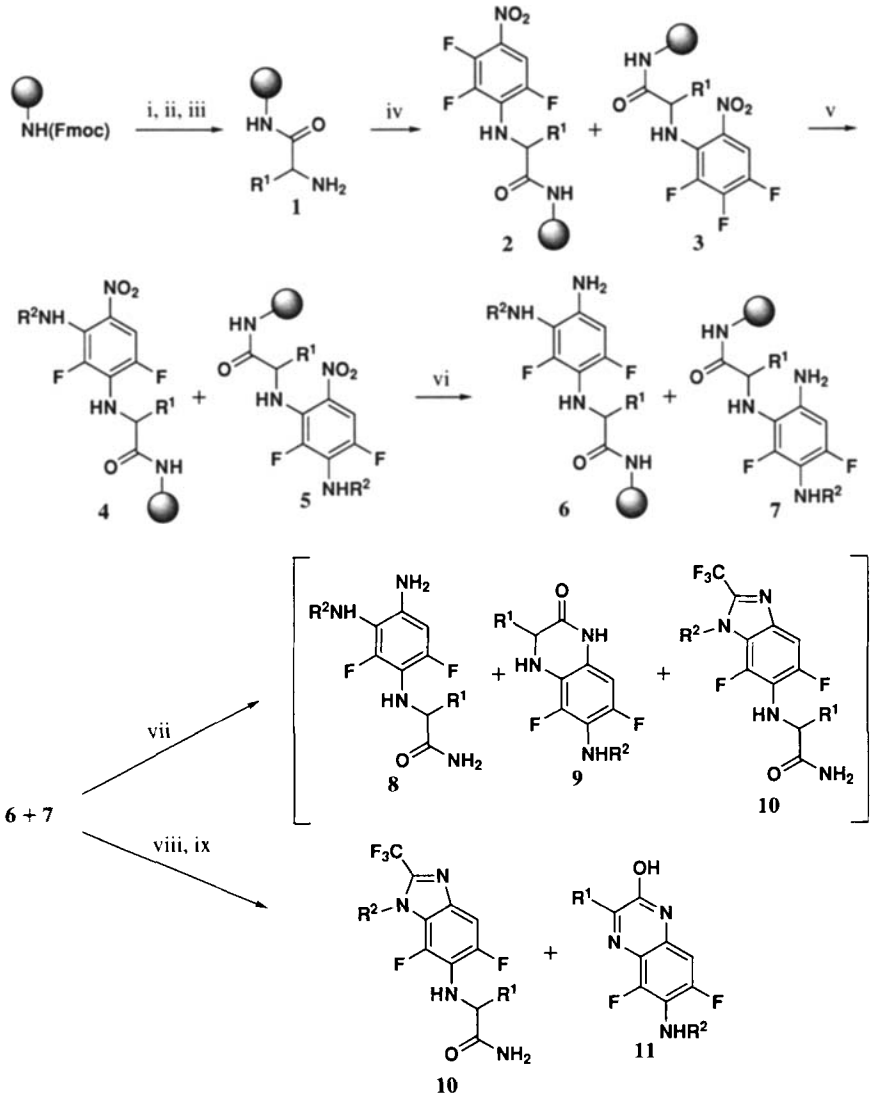
In the process of the synthesis of fluoro heterocycles on solid support from 6-nitro-2,3,4,5-tetrafluorobenzoic acid, we found 2,3,4,5-tetrafluoronitrobenzene (TFNB) would be a novel scaffold to construct heterocyclic compounds. According to "fluoronitroaromatics scaffold" strategies, theoretically abundant mono-, bi-, and macrocycles would have been prepared from this versatile scaffold.[18] As shown in *Scheme 1*, valine



Knorr resin

Fig. 1

was prepared as a model amino acid pre-attached to Knorr resin to operate our solid-phase synthesis. When resin-bound valine (**1**) was shaken with an excess of 2,3,4,5-tetrafluoronitrobenzene (TFNB) in dimethylformamide (DMF), two resin-bound regioisomers **2** and **3** (R^1 =



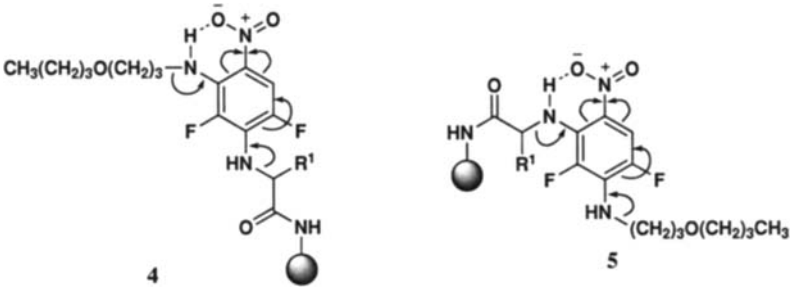
R^1 = $CH(CH_3)_2$, R^2 = $(CH_2)_3O(CH_2)_3CH_3$; i) 20% piperidine/DMF; ii) R^1CHNH(Fmoc)COOH, HOBt, DIC/DMF; iii) 20% piperidine/DMF; iv) 2,3,4,5-F_4-NO_2C_6H/DMF; (v) R^2NH_2/DMF; (vi) 2M $SnCl_2$•$2H_2O$/2M NMM/DMF; vii) 20% TFA/DCM; viii) 20% TFA/DCM, then reflux; ix) reflux in methanol

Scheme 1

$CH(CH_3)_2$) were formed to display a "one-bead-two-compound" feature. Just as expected, the reaction appeared to occur at either 2- or 4-position to provide two isomeric products from each bead. To monitor the solid-phase procedure, about 3 mg of polymer-supported intermediates were cleaved in order to carry out LC and/or LC-MS analysis in each step.

In a subsequent step, displacement of the second active fluorine at 2- or 4-position with α-amino ester became somewhat problematic owing to the weak nucleophilicity of the amino ester and the deactivation by the amino groups on **2** and **3**. Nucleophilic attack of α-amino ester proved to be incomplete in the presence of diisopropylethylamine (DIPEA), even under forcing conditions (20 equiv. α-amino ester, 70°C, 16 h). The cleavage products showed very complicated LC-MS analyses. However, when a primary aliphatic amine such as 3-butoxy-1-propylamine was used as a strong nucleophilic agent, the second displacement occurred smoothly at room temperature to afford the benzenediamines **4** and **5**.

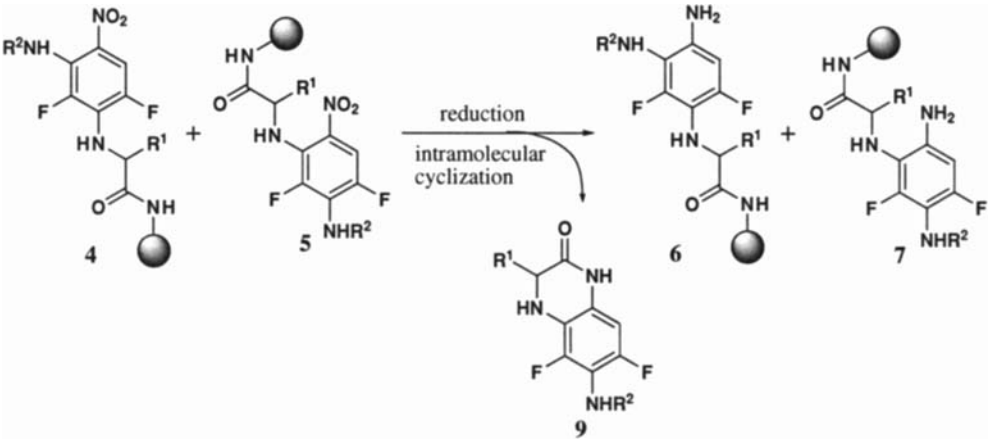
In solid-phase chemistry, tin(II) chloride is generally used as a reducing agent for the reduction of aryl nitro groups to arylamines because of its reducing ability and excellent solubility in DMF or *N*-methyl-2-pyrrolidinone (NMP). However, reaction of **4** and **5** with $SnCl_2 \cdot 2H_2O$/DMF failed to give the anticipated **6** and **7**, even upon prolonged time. In the absence of electron-donating groups on aryl ring, nitrobenzenes can be successfully reduced on solid support.[13-15, 19-23] The difficulty for reduction of the nitro group has also been encountered in other cases on solid support.[4, 24] It is believed that two electron-donating amino groups in **4** and **5** and intramolecular hydrogen bonding make that the nitro groups remarkably resistant to reduction (*Fig. 2*).



Electron-donating effect and intramolecular hydrogen bond of **4** and **5**

Fig. 2

$SnCl_2 \cdot 2H_2O$/*N*-methylmorpholine (NMM)/NMP reduction system had been first applied in the treatment of the resin-bound 1,5-diamino-2,4-dinitrobenzene[25] and it was gratifying to find that not only $SnCl_2 \cdot 2H_2O$/NMM reduces **4** and **5** but also that 2 M $SnCl_2 \cdot 2H_2O$/2 M NMM/DMF, 2 M $SnCl_2 \cdot 2H_2O$/2 M DIPEA/DMF, and 2 M $SnCl_2 \cdot 2H_2O$/2 M Et_3N/DMF were equally effective in reducing the nitro groups of **4** and **5** to corresponding amines at room temperature overnight. To rationalize this outstanding reducing ability, it was reasoned that the strong *N*-bases neutralize the strong Lewis acid tin(IV) chloride generated during the reaction, thus enhancing the reducing power of tin(II) chloride. It was noticed that, since Knorr resin is highly acid labile, the basic environment of $SnCl_2 \cdot 2H_2O$/tertiary amine suppresses the possible loss of the resin as the cyclized product **9** (*Scheme 2*).[26]



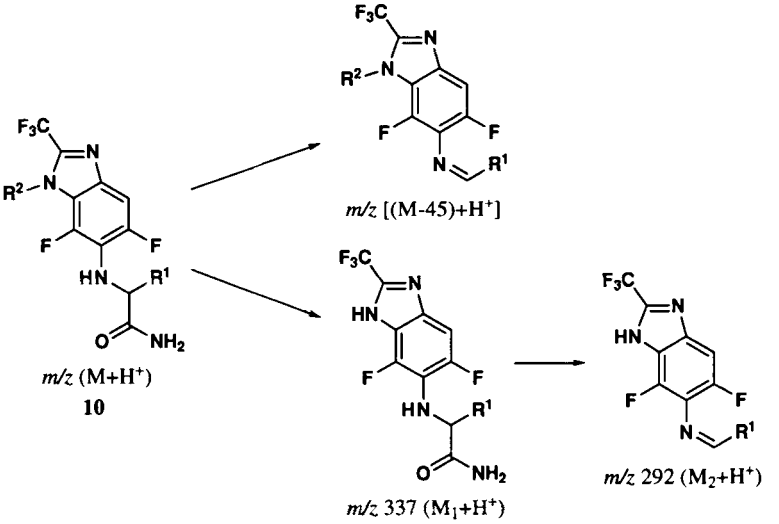
Possible product loss during reduction step

Scheme 2

Unexpectedly, besides the anticipated **8** and **9**, unexpected concomitant product **10** was unavoidably generated during the cleavage of **6** and **7** using trifluoroacetic acid (TFA) as shown by LC-ESI-MS monitoring (*Scheme 1*). In order to investigate its mode of formation, other primary aliphatic amines (R^2NH_2) were made to undergo the same reactions and a consistent pattern was observed. When quasi-molecular ion peak ($M+H^+$) of **10** (as well as other primary aliphatic amine sets) was bombarded with ESI-MS^2 manner to occur neutral loss, the common fragment ions of 337 and 292, and a daughter fragment of M-45 could be observed in each case. This fact implies that **10** possesses the same skeleton after splitting building block (R^2) in each set, and **10** should be considered a product during the cleavage of **6** and **7** using TFA. A possible decomposition pathway of **10** is shown in *Scheme 3*. Just after **10** was separated with reverse-phase chromatography to obtain its ^1H and ^{13}C NMR spectra, the trifluoromethylbenzimidazole skeleton was unequivocally confirmed, particularly by the presence of a quadruple split at *ca.* 118.7 ppm as a diagnostic chemical shift of trifluoromethyl group in ^{13}C NMR spectra of **10**. Thus it was easy to understand this decomposition pattern of **10** under ESI-MS^2 in *Scheme 3*. The cleavage of **6** and **7** resulted in **8** and intramolecularly cyclized product **9**. Apparently, benzimidazoles **10** derived from benzenetriamines **8** and TFA during cleavage. A mixture of **8**, **9** and **10** was finally obtained without any trace of **4** and **5** as determined by LC-MS analysis.

On account of its non-heterocyclic and extremely oxidizable nature, it was necessary to convert **8** into heterocyclic **10** making use of above cleavage chemistry. We also believed that quinoxalinones **9** were exceedingly susceptible to oxidative dehydrogenation during storage and work-up (*Scheme 4*).[13] Consequently, we developed a cleavage process to finally procure the desired structures **10** and **11** in *Scheme 1*. Compounds **6** and **7** were first cleaved with TFA at reflux under an argon atmosphere for 4 h to accelerate the formation of **10**, and then the mixture was refluxed for 10 h in methanol to accelerate the dehydrogenation of **9**. The resulting trifluo-

romethylbenzimidazoles **10** and 2-quinoxalinols **11** were easily separated with reverse-phase column chromatography.

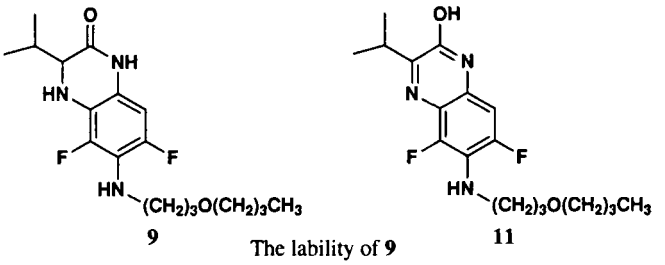


$R^1 = CH(CH_3)_2$, $R^2 = (CH_2)_3O(CH_2)_3CH_3$, $(CH_2)_2Ph$, $(CH_2)_3Ph$, $(CH_2)_3CH_3$

A proposed decomposition pathway of **10** standing ESI-MS^2

Scheme 3

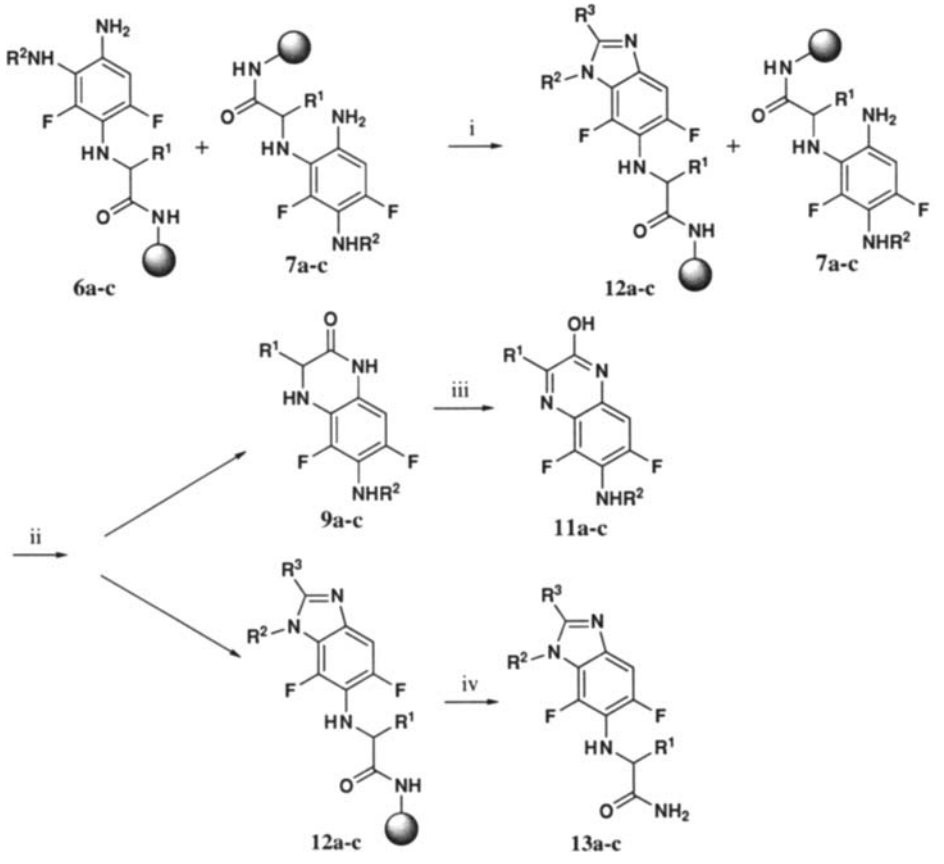
Although we successfully acquired the drug-like skeletons difluorobenzimidazoles **10** and difluoro-2-quinoxalinols **11**, it would well be warranted to introduce further building block (R^3) for molecular diversity. As the presence of the *o*-benzenediamine moiety in **6** and **7** would easily allow the creation of many heterocyclic structures, the synthesis of versatile pharmacophore benzimidazoles became our principal goal. Originally we wished to obtain the same two skeletons of benzimidazoles at each bead depending on reaction of *o*-benzenediamines and aldehydes.



Scheme 4

Upon completion of the reduction of **4** and **5**, subsequent reaction with aldehydes should immediately occur due to the lability of **6** and **7** (*Scheme 5*). Unfortunately, under our experimental conditions, only the benzenetriamines **6** effectively reacted with aldehydes to yield

12, and the benzenetriamines **7** did not react with aldehydes at room temperature possibly because of steric factors. Cleavage of **12** and **7** with TFA afforded the difluorobenzimidazoles **13** and intramolecularly cyclized product **9**. Refluxing the mixture in methanol induced dehydrogenation of **9** to afford final difluoro-2-quinoxalinols **11**. This procedure might be suitable in combinatorial chemistry as a protocol of "one-procedure-two-skeleton". Thus we obtained a mixture of **13** and **11** and developed a method of "one-bead-two-compound".



a) $R^1 = CH(CH_3)_2$, $R^2 = (CH_2)_3O(CH_2)_3CH_3$, $R^3 = 3,4,5\text{-}(CH_3O)_3C_6H_2$; b) $R^1 = CH(CH_3)_2$, $R^2 = (CH_2)_3CH_3$, $R^3 = CH_2Ph$; c) $R^1 = CH(CH_3)_2$, $R2 = (CH_2)_3Ph$, $R^3 = 3,4,5\text{-}(CH_3O)_3C_6H_2$; i) R_3CHO/2% AcOH/DMF; ii) 10% AcOH/DMF; iii) CH_3OH, reflux; iv) 20% TFA/DCM

Scheme 5

To meet the current development of "one-well-one-compound" for parallel preparation of molecular library, a method of simple separation was investigated. Since the Knorr resin is highly acid labile,[27] it occurred to us that, under appropriate cleavage conditions after the formation of **12**, it might be possible to release **9** in advance from the resin by virtue of a tendency of intramolecular cyclization. We successfully achieved the separation of **11** and **13** *via* two cleav-

ages in *Scheme 5*. While **12** was readily obtained from **6** and aldehydes in 2% AcOH/DMF, the non-reactive **7** did not undergo intramolecular cyclization under these weak acid conditions. Furthermore, while **7** was gently cleaved with 10% AcOH/DMF, the stable **12** remained nearly unaffected, with minimal loss. After cleavage of **7** and separation of **9**, **12** was cleaved using TFA to remove the unreacted **13**. Finally, the dehydrogenation of **9** gave **11**.

In summary, we have successfully prepared two fluoro heterocyclic skeletons with a "one-bead-two-compound" method. A polyfluoro scaffold, such as TFNB containing 2,4-difluoronitrobenzene moiety, was indispensable for the method in view of its double reactive sites. Meanwhile by means of a method of intramolecularly cyclizative cleavage, a simple strategy of separation has been established to accord with "one-well-one-compound" production. Moreover, this method would make other synthetic transformations possible for preparations of fluoro heterocyclic compounds.[18]

EXPERIMENTAL SECTION

Knorr resin and other chemical reagents for solid-phase synthesis were purchased from GL Biochem (Shanghai) Ltd. TFNB was prepared *via* a facile decarboxylation of 6-nitro-2,3,4,5-tetrafluorobenzoic acid according to the literature.[28] All solvents were purified *via* standard drying and distillation procedures. Melting points are uncorrected. Elemental analyses were performed on a PE-2400 elemental Analyzer. ^{1}H and ^{13}C NMR were recorded on Varian INOVA 500 instrument in $CDCl_3$. ^{1}H and ^{13}C spectra were referenced using residual solvent or solvent peaks as internal standard. High-resolution mass spectra were obtained from an AutoSpec Ultima-Tof tandem double-focusing magnetic mass spectrometer. The matrix was a mixture of glycerol for FAB-MS. LC-MS were carried out on a Waters 600 system with Surveyor PDA detector, Surveyor LC pump, Surveyor autosampler, SymmetryShield C18 3.9 x 150 mm column and 5 min gradient from 95% water (0.1% TFA) to 95% acetonitrile (0.1% TFA) at 1.0 mL/min flow rate and 10:1 split ratio, and a Thermo Finnigan-LCQ Advantage MS/MS system driven electrospray ionization (ESI) instrument. The cone potentials of ESI were installed in 20 V and 30 V for MS and MS^2, respectively.

Typical Procedure for the Preparation of 10 and 11.- Knorr resin (200 mg, 100-200 mesh, loading 0.65 mmol/g) was swelled and deprotected twice with 20% piperidine/DMF for 20 min. After the resin was washed thoroughly with DMF, a DMF solution of Fmoc-Val-OH amino acid (111 mg, 2.5 equiv.), hydrated 1-hydroxybenzotriazole ($HOBt•H_2O$, 50 mg, 2.5 equiv.) and diisopropylcarbodiimide (DIC, 50 mg, 3.0 equiv.) was added to the resin and shaken at 25°C overnight to complete the reaction, and then the resin was washed with DMF. Again the resin was deprotected twice with 20% piperidine/DMF for 20 min, and washed thoroughly with DMF (4 mL x 3), CH_3OH (4 mL x 3) and dichloromethane (DCM, 4 mL x 3). Finally the resin was dried under vacuum for 3 h to afford **1**.

A large excess of 2,3,4,5-tetrafluoronitrobenzene (127 mg, 5.0 equiv.) in DMF (4 mL) was added to the resin and the reaction was shaken for 3 h at 25°C. The resin was washed with DMF, CH_3OH, DCM, and Et_2O to provide the resin–bound isomers **2** and **3**.

A large excess of 3-butoxy-1-propylamine (131 mg, 10.0 equiv.) in DMF (4 mL) solution was added to the resin and the reaction was shaken at 25°C overnight. Then the resin was washed with DMF, DCM, CH_3OH and Et_2O to provide the benzenediamines **4** and **5**.

The resin was suspended in a 2 M $SnCl_2 \cdot 2H_2O$/2 M NMM/DMF solution (4 mL), and under an argon atmosphere shaken at 25°C overnight. The resin was washed thoroughly with DMF, DCM, CH_3OH and Et_2O to furnish the benzenetriamines **6** and **7**.

The resins was cleaved with 20% TAF/DCM (2 mL) for 15 min at 25°C, and then the cleaved resin was washed with DCM (2 mL x 2) and CH_3OH (2 mL x 2). The collected cocktail was refluxed for 4 h under an argon atmosphere. Afterward the concentrated residue was refluxed in methanol for 10 h to give a mixture of **10** and **11**. By a gradient elution from 10% MeCN/H_2O to 90% MeCN/H_2O in 10% alternation, the mixture was separated with reverse-phase column chromatography to present **10** and **11**. The isolated yields were based on the original loading of Knorr resin.

2-[1-(3-Butoxypropyl)-5,7-difluoro-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-6-yl]amino-3-methylbutanamide (10), (14.5 mg, 25%), yellow solid, mp 128.3°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (3H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.06 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 1.35 (2H, sxt, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.53 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 2.11 (2H, qui, $J_1 = J_2$ = 7.0 Hz, $OCH_2CH_2CH_2N$), 2.43 (1H, m, $CHCH(CH_3)_2$), 3.39 (2H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 3.49 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2N$), 3.85 (1H, d, *J* = 3.5 Hz, $CHCH(CH_3)_2$), 4.46 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2N$), 5.67 (1H, s, CONHH), 6.54 (1H, s, CONHH), 7.33 (1H, d, $^2J_{H\text{-}F}$ = 11.0 Hz, Ar-*H*), NH not observed. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 17.2, 19.3 (2 x CH_3), 31.4, 31.5, 31.7, 44.7, 66.4, 67.4, 70.8, 103.1, 118.7 (q, $^1J_{C\text{-}F}$ = 269.7 Hz, CF_3), 121.6, 124.0, 134.7, 138.2 (d, $^1J_{C\text{-}F}$ = 240.8 Hz), 141.0, 151.6 (d, $^1J_{C\text{-}F}$ = 237.0 Hz), 175.4. MS-ESI: *m/z* 451.3 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{20}H_{28}F_5N_4O_2$: 451.2132; found: 451.2278.

Anal. Calcd for $C_{20}H_{27}F_5N_4O_2$: C, 53.33; H, 6.04. Found: C, 53.12; H, 6.31.

6-(3-Butoxypropyl)amino-5,7-difluoro-3-isopropyl-2-quinoxalinol (11), (22.3 mg, 49%), white solid, mp 132.8°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (3H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.35 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 1.40 (2H, sxt, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.59 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.87 (2H, qui, $J_1 = J_2$ = 7.0 Hz, $OCH_2CH_2CH_2N$), 3.43 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2N$), 3.49 (2H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 3.55 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2NH$), 3.61 (1H, sep, *J* = 7.5 Hz, $CH(CH_3)_2$), 6.82 (1H, d, $^2J_{F\text{-}H}$ = 11.0 Hz, Ar-*H*), 12.08 (1H, bs, O*H*), NH not observed. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 19.3, 20.1 (2 x CH_3), 30.2, 31.0, 31.8, 45.2, 69.3, 71.1, 97.2, 120.7, 123.2, 123.6, 147.7 (d, $^1J_{C\text{-}F}$ = 248.4 Hz), 154.7 (d, $^1J_{C\text{-}F}$ = 246.1 Hz), 156.0, 164.5. MS-ESI: *m/z* 354.2 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{18}H_{26}F_2N_3O_2$: 354.1993; found: 354.2009.

Anal. Calcd for $C_{20}H_{25}F_2N_3O_2$: C, 61.17; H, 7.13. Found: C, 61.44; H, 7.39.

Typical Procedure for the Preparation of 11 and 13.- A large excess of aldehyde (10.0 equiv.), such as 3,4,5-trimethoxybenzaldehyde or 2-phenylacetaldehyde in 2% AcOH/DMF solution (4 mL) was added to the fresh resin–bound benzenetriamines **6** and **7** which were generated from 200 mg Knorr resin, Fmoc-Val-OH amino acid, and amine (10.0 equiv.) such as 3-butoxy-1-propylamine, n-butyl amine or 3-phenyl-1-propylamine. The reaction was shaken at 25°C for 72 h and then the resin was washed with DMF, DCM, CH_3OH and Et_2O to afford the benzimidazoles **12** and the non-reactive **7**.

The resin was suspended in 10% AcOH/DMF solution (4 mL) and shaken at 25°C for 48 h to mildly cleave **7**. The solution was aspirated and collected, and the resin was washed with DMF (1 mL x 2), DCM (1 mL x 2) and CH_3OH (1 mL x 2). The combined cocktail was concentrated under vacuum, and then the residue was refluxed in methanol for 10 h *via* the dehydrogenation of **9** to provide **11**. The residual resin was washed thoroughly with DMF, DCM, CH_3OH and Et_2O to furnish the pure **12**.

The residual resin was cleaved with 20% TAF/DCM (2 mL) for 15 min at 25°C, and then the cleaved resin was washed with DCM (2 mL x 2) and CH_3OH (2 mL x 2). The collected cocktail was concentrated under vacuum to dryness to offer **13**.

6-(3-Butoxypropyl)amino-5,7-difluoro-3-isopropyl-2-quinoxalinol (11a), (22.1 mg, 49%), white solid, mp 129.1-131.4°C. Its NMR and MS data are the same as **11**.

2-[1-(3-Butoxypropyl)-5,7-difluoro-2-(3,4,5-trimethoxyphenyl)-1*H*-benzo[*d*]imidazol-6-yl]-amino-3-methylbutanamide (13a), (20.2 mg, 28%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.06 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 1.24 (2H, sxt, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 1.40 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 2.15 (2H, qui, $J_1 = J_2$ = 7.0 Hz, $OCH_2CH_2CH_2N$), 2.56 (1H, m, $CHCH(CH_3)_2$), 3.24 (2H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2O$), 3.38 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2N$), 3.89 (1H, d, *J* = 3.5 Hz, $CHCH(CH_3)_2$), 3.92 (6H, s, Ar-$(OCH_3)_2$), 3.95 (3H, s, Ar-OCH_3), 4.58 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_2N$), 6.23 (1H, s, CONHH), 6.72 (1H, s, CONHH), 6.97 (2H, s, Ar-H_2), 7.61 (1H, d, $^2J_{F\text{-}H}$ = 11.0 Hz, Ar-H), NH not observed. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 17.2, 19.1 (2 x CH_3), 31.1, 31.4, 31.6, 45.7, 56.5 (2 x CH_3), 61.0, 66.1, 66.8, 71.0, 99.6, 107.1 (2 x CH_{Ar}), 119.3, 124.3, 126.4, 139.0 (d, $^1J_{C\text{-}F}$ = 240.8 Hz), 143.2, 143.6, 152.4 (d, $^1J_{C\text{-}F}$ = 237.0 Hz), 153.9 (2 x CH_{Ar}), 161.7, 176.0. MS-ESI: *m/z* 549.3 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{28}H_{39}F_2N_4O_5$: 549.2889; found: 549.2923.

Anal. Calcd for $C_{28}H_{38}F_2N_4O_5$: C, 61.37; H, 7.15. Found: C, 61.10; H, 7.41.

6-(*n*-Butylamino)-5,7-difluoro-3-isopropyl-2-quinoxalinol (11b), (18.6 mg, 49%), white solid, mp 141.0-144.0°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.36 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 1.43 (2H, sxt, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.55 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 3.36 (2H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2NH$), 3.53 (1H, bs, NH), 3.62 (1H, sep, *J* = 7.0 Hz, $CH(CH_3)_2$), 6.82 (1H, d, $^2J_{F\text{-}H}$ = 11.0 Hz, Ar-H), 12.17 (1H,

bs, O*H*). MS-ESI: *m/z* 296.2 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{15}H_{20}F_2N_3O$: 296.1574; found: 296.1792.

Anal. Calcd for $C_{15}H_{19}F_2N_3O$: C, 61.00; H, 6.48. Found: C, 59.87; H, 6.61.

2-[(2-Benzyl-1-butyl-5,7-difluoro-1*H*-benzo[*d*]imidazol-6-yl)amino-3-methylbutanamide (13b), (15.3 mg, 28%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3H, t, *J* = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.06 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 1.25 (2H, sxt, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.47 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_3CH_2CH_2CH_2$), 2.45 (1H, m, $CHCH(CH_3)_2$), 3.90 (1H, d, *J* = 3.5 Hz, $CHCH(CH_3)_2$), 4.03 (2H, t, *J* = 7.5Hz, $CH_3CH_2CH_2CH_2N$), 4.24 (2H, s, CH_2Ph), 5.53 (1H, s, CONHH), 6.73 (1H, s, CONHH), 7.23 (2H, d, *J* = 7.5Hz, Ar-H_2), 7.29 (2H, q, $J_1 = J_2$ = 7.5 Hz, Ar-H_2), 7.51 (1H, m, Ar-*H*), 7.64 (1H, d, $^2J_{F\text{-}H}$ = 11.0 Hz, Ar-*H*), NH not observed. MS-ESI: *m/z* 415.3 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{23}H_{29}F_2N_4O$: 415.2309; found: 415.2287.

Anal. Calcd for $C_{23}H_{28}F_2N_4O$: C, 66.65; H, 6.81. Found: C, 66.51; H, 6.67.

5,7-Difluoro-3-isopropyl-6-(3-phenylpropyl)amino-2-quinoxalinol (11c), (22.7 mg, 49%), white solid, mp 162.2-163.7°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$), 1.93 (2H, qui, $J_1 = J_2$ = 7.5 Hz, $CH_2CH_2CH_2$), 2.72 (2H, t, *J* = 7.5 Hz, $PhCH_2CH_2CH_2$), 3.38 (2H, t, *J* = 7.5Hz, $CH_2CH_2CH_2N$), 3.56 (1H, bs, N*H*), 3.61 (1H, sep, *J* = 6.5 Hz, $CH(CH_3)_2$), 6.80 (1H, d, $^2J_{F\text{-}H}$ = 11.0 Hz, Ar-*H*), 7.18 (2H, d, *J* = 7.5 Hz, Ar-H_2), 7.20 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.28 (2H, dd, *J* = 7.5 Hz, *J* = 7.5 Hz, Ar-H_2), 12.56 (1H, bs, O*H*). MS-ESI: *m/z* 358.2 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{20}H_{22}F_2N_3O$: 358.1731; found: 358.1844. *Anal.* Calcd for $C_{20}H_{21}F_2N_3O$: C, 67.21; H, 5.92. Found: C, 66.97; H, 6.11.

2-[5,7-Difluoro-1-(3-phenylpropyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-benzo[*d*]imidazol-6-yl]-amino-3- methylbutanamide (13c), (21.0 mg, 29%), yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (6H, d, *J* = 7.5 Hz, $CH(CH_3)_2$), 2.02 (2H, qui, $J_1 = J_2$ = 7.5Hz, $PhCH_2CH_2CH_2$), 2.42 (m, 1 H, $CHCH(CH_3)_2$), 2.87 (2H, t, *J* = 7.5 Hz, $PhCH_2CH_2CH_2$), 3.60 (2H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2N$), 3.85 (1H, d, *J* = 4.0 Hz, $CHCH(CH_3)_2$), 3.90 (6H, s, Ar-$(OCH_3)_2$), 3.94 (3H, s, Ar-OCH_3), 5.31 (1H, s, CONHH), 6.44 (1H, s, CONHH), 6.77 (2H, s, Ar-H_2), 6.83 (2H, d, *J* = 7.5 Hz, Ar-H_2), 7.13 (1H, t, *J* = 7.0 Hz, Ar-H_2), 7.27 (2H, dd, *J* = 7.5 Hz, *J* = 7.0 Hz, Ar-H_2), 7.66 (1H, d, $^2J_{H\text{-}F}$ = 11.0 Hz, Ar-*H*), NH not observed. MS-ESI: *m/z* 553.3 [M+H$^+$]. HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{30}H_{35}F_2N_4O_4$: 553.2626; found: 553.2833.

Anal. Calcd for $C_{30}H_{34}F_2N_4O_4$: C, 65.20; H, 6.20. Found: C, 65.02; H, 6.43.

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